Small Blood Vessels: Big Health Problems
National Institute of Neurological Disorders and Stroke Update

Meghan Mott, PhD; Katherine Pahigianis, PhD; Walter Koroshetz, MD

Because of the aging of our population, the burden of dementia is projected to double worldwide in the next generation, making it one of the greatest challenges faced by healthcare systems globally. Cerebral small-vessel disease is a major contributor to age-related cognitive impairment. Recent epidemiological research provides evidence that hypertension, cerebral infarction, and diffuse white matter disease (leukoaraiosis) are associated with increased risk of cognitive impairment. Most people who die with a diagnosis of dementia have a mixture of Alzheimer and vascular disease. Studies from Europe have reported recent decreases in dementia risk as might be expected from the decreased stroke risk that occurred over a similar time period.

Small-Vessel Disease, Stroke, and Cognitive Decline

Although these correlative studies are important, we have not yet established causality. Besides control of blood pressure, there are no targeted therapies that exist for small-vessel disease. The National Institute of Neurological Disorders and Stroke (NINDS)–funded Secondary Prevention of Small Subcortical Strokes study showed a strong trend toward a decrease in recurrent stroke with aggressive blood pressure lowering below a target of 130 mm Hg compared with below 140 mm Hg. This, together with the totality of data linking aggressive blood pressure lowering to lower stroke risk, should serve as a warning to those advocating loosening of the threshold for treatment to 150 mm Hg. The contribution of vascular pathology to the biology of Alzheimer disease and the interaction between Alzheimer biology and small-vessel disease is incompletely understood. Although more difficult to quantify, there would likely be negative consequences from loosening blood pressure targets on cognitive impairment and dementia.

Community Focus on Small-Vessel Disease

For 10 years, the Stroke Progress Review Group (http://www.ninds.nih.gov/about_ninds/groups/stroke_prg/01-2012-stroke-prg-report.html) stressed the concept of the neurovascular unit in which neurons, glia, endothelial cells, pericytes, cerebrospinal fluid, and immune cells (both inside and outside the vessel) integrate their activities. Although critically important because of its relevance to normal brain function and stroke, the tie between neurovascular biology, vascular cognitive impairment and dementia have recently elevated this area of research to new prominence.

The NINDS Stroke Planning process also identified prevention of vascular cognitive impairment as one of their 9 top recommendations (http://www.ninds.nih.gov/find_people/ninds/OSPP/Stroke-Research-Priorities-Meeting-2012.html#Toc345350712). The report’s vascular cognitive impairment recommendations address both preclinical and clinical scientific opportunities by (1) identifying key biological pathways that promote small-vessel disease and agents that interfere with them, as well as (2) developing pilot clinical trials of targeted therapies using imaging biomarker outcomes. One of the proposal’s key goals is to investigate the interactions between small-vessel disease, ischemia, and Alzheimer disease biology.

Congress’s National Alzheimer’s Project Act created a national strategic plan to address the rapidly escalating Alzheimer disease crisis (http://www.gpo.gov/fdsys/pkg/PLAW-111publ375/pdf/PLAW-111publ375.pdf). The leadership appropriately considered dementia more broadly and charged NINDS to work with the National Institute on Aging and others to incorporate Alzheimer Disease Related Dementias into the National Plan to address Alzheimer disease (http://aspe.hhs.gov/daltpc/napa). In response, NINDS convened panels of experts and conducted a 2-day public conference in 2013 to develop research priorities addressing Alzheimer Disease Related Dementias in 5 topic areas, including vascular dementia (http://www.ninds.nih.gov/funding/areas/neurodegeneration/workshops/adr2013/booklet-and-recommendations_508comp.pdf). The emphasis on small-vessel disease focused on basic mechanisms, experimental models, and human-based studies. Priorities included the development of more informative experimental models and the development and validation of noninvasive biomarkers of tissue injury and vessel disease. As an outcome of these planning efforts, NINDS partnered with the National Institute on Aging, which published a Request for Applications in August for interdisciplinary research to understand the vascular contributions to Alzheimer disease (http://grants.nih.gov/grants-guide/rfa-files/RFA-AG-15-010.html). The due date for applications is February 3, 2015.

Small-vessel disease in the brain is likely to have features in common with small-vessel disease in other organs. To enable multidisciplinary discussion and information sharing, a trans–National Institutes of Health small-vessel working group was formed with representatives from many of National Institutes...
of Health’s institutes and centers. The group recently con-vened a 2-day conference of scientists and clinical investiga-tors from diverse areas of small blood vessel research (brain, heart, lung, kidney, muscle, eye, and skin) to share their latest discoveries and tools (https://meetings.ninds.nih.gov/index.cfm?event=agenda&ID=8225).

**Future Outlook**
The effect of successfully identifying ≥1 treatments that slow progression of small-vessel and microvascular disease that contributes to dementia would be extraordinarily high.

However, a better understanding of small-vessel disease requires sustained and concerted effort from an expanded, multidisciplinary research community that is connected to the science of small vessels in other organs and to the biology of neurodegeneration. Although more difficult than the study of surface vessels, the problem of diffuse white matter disease calls for a special focus on age-related, hypertensive disease in the small penetrator vessels that supply the deep white matter and its interaction with myelin biology and the immune system. What were once unsolvable problems may now be approached with a host of newly available optical imaging and genetic tools. Relatedly, the technologies under development as part of the Brain Research through Advancing Innovative Neurotechnologies initiative should also be exploited for their ability to transform research on the role of the neurovascular unit in health and disease (http://www.nih.gov/science/brain/index.htm).

**Disclosures**
None.

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